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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/918,407	08/26/97	ROTH J	INGN:050/HYL

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ARNOLD WHITE AND DURKEE
P O BOX 4433
HOUSTON TX 77210-4433

EXAMINER	
SANDALS,W	
ART UNIT	PAPER NUMBER
1636	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/918,407	Applicant(s) Roth et al.
	Examiner WILLIAM SANDALS	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 29, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20, 22-26, 32-61, 77-79, 83-91, 96-101, 111, 112, 115-120, ar* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-20, 22-26, 32-61, 77-79, 83-91, 96-101, 111, 112, 115-120, and 12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Response to Arguments

1. In view of the amendments filed on May 22, 2000, PROSECUTION IS HEREBY REOPENED. New grounds or rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(a) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(b) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claim Objections

2. Claim 38 is objected to because of the following informalities: claim 38 recites "wherein said recombinant vector is a recombinant adenonviral vector is present". This language is confusing to read because the section which recites "said recombinant vector" seems to be superfluous. Deleting "recombinant vector is a" from the passage would correct this defect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-20, 22-26, 32-41, 46-61, 77-79, 83-91, 96-101, 111, 112, 115-120, 128-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practice of the invention in a mouse model provides no nexus exists for enablement for practicing the invention in a non-model animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method and composition for practice of a method of reducing the growth rate of a tumor by introducing a p53-expressing gene into a tumor while exposing the tumor to a DNA damaging agent. The combination then inhibits the growth of the tumor cells exposed to the combination of p53 and a DNA damaging agent.

a- The amount of experimentation required to practice the invention in the full scope of the claims would involve the development of a method for treatment of tumors in an non-mouse model animal with a gene expressing p53 and a DNA damaging agent.

b- There are only working examples provided in a mouse model system, and only limited prophetic guidance.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

f- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

g- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims. (all references are of record)

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-11, 19, 20, 25, 35-39, 45, 51-61, 77-79, 115-120, 128-130 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 2-3, 33, 34, 39 are rejected because there is no clear nexus between the "DNA damaging agent" of claim 1 and the list provided in claim 2. A link between the "DNA damaging agent" of claim 1 which states that the list provided in claim 2 is in fact a list of "DNA damaging agents" would cure this defect. For purposes of examination, it is assumed that there is a nexus between the claimed elements.

8. Claim 4 is rejected because it broadens the scope of claim 1. A dependent claim must further limit the independent claim.

9. Claims 4-11, 19, 20, 25, 33-39, 77-79, 128-130 are unclear because claim 4 recites a recombinant vector that expressed a functional p53 protein. There is no linking language to relate that the "p53 gene" of independent claim 1 is the same as the "expressed functional p53 functional protein" of claim 4. A clear statement which links or distinguishes between the two elements is necessary to clarify the claim. For purposes of examination, it is assumed that the claimed elements of claims 1 and 4 are the same element.

10. Claim 5 recites the limitation "said p53-expressing recombinant" in line 1. There is insufficient antecedent basis for this limitation in the claim.

11. Claim 5 recites a "plasmid **or** (emphasis added) a plasmid within a liposome , a retroviral vector, an AAV vector, **or** (emphasis added) a recombinant adenoviral vector". The use of "or" in the two locations provides an ambiguity as to what is being claimed. It is not clear what is meant by these limitations, since one would not know whether it is one limitation or the other limitation, or both, which is intended to be part of the claim.

12. Claim 6 recites the limitation "said p53-expressing recombinant" in line 1. There is insufficient antecedent basis for this limitation in the claim.

13. Claim 7 recites the limitation "said p53-expressing recombinant" in line 1. There is insufficient antecedent basis for this limitation in the claim.

14. Claim 8 recites the limitation "the cytomegalovirus" in line 2. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 8 recites the limitation "the SV40 early polyadenylation signal" in line 2. There is insufficient antecedent basis for this limitation in the claim.

16. Claim 9 recites the limitation "the p53 expression region" in line 2. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 10 recites the limitation "the p53 expression region" in line 2. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 10 recites the limitation "the EIA and EIB regions" in line 1. There is insufficient antecedent basis for this limitation in the claim.

19. Claims 11, 38, 39, 45 and 39 recite the limitation "a recombinant adenoviral vector is present within a recombinant adenovirus". It is unclear how an adenovirus vector is different from the adenovirus since the two elements would intuitively be one in the same.

20. Claims 51-61, 115-118 are dependent upon claim 1, claims 52-61 are dependent upon claim 51. Claim 1 recites a "DNA damaging agent". Claim 51 recites a "DNA damaging compound". It is unclear how the "DNA damaging compound" of claim 51 relates to the "DNA damaging agent" of independent claim 1 and further dependent claims 52-61, 115-118. Is the "DNA damaging compound" the same as the "DNA damaging agent" or some other entity? For purposes of examination, it is assumed that the claimed elements are the same.

21. Claims 86-91 recite the limitation "the period" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 32 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by each of Wills et al. or Lowe et al. (both of record)

Wills et al. (see the entire article) taught a composition for killing a tumor cell comprising contacting a tumor cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, gamma irradiation, or etoposide. An adenoviral vector expressing the p53 gene may be deleted in E1A or E1B, which contained a CMV promoter. The p53 gene was expressed in tumors in animal models.

Lowe et al. (see the entire article) taught a composition for killing a tumor cell comprising contacting a tumor cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, gamma irradiation, or etoposide. The p53 gene was in a non-viral vector, which may be a naked DNA plasmid with a polyadenylation signal.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 1-26, 32-41, 46-61, 77-79, 83-91, 96-101, 111-120, 127-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gregory et al. in view of Lowe et al., Clarke et al., Wills et al., and Tischler et al. (all of record)

The claims are drawn to a method of reducing the growth rate of a tumor by contacting the cells of a tumor with a gene encoding a functional p53 protein and contacting the cells of the tumor with a DNA damaging agent. The p53 gene may be present in a plasmid, which may be a naked DNA plasmid or a plasmid in a liposome or the p53 gene may be in an adenoviral vector, where the adenoviral vector may be deleted for EIA and EIB. The DNA damaging agent may be X-rays, UV irradiation, gamma irradiation, microwaves, adriamycin, 5-flourouracil, etoposide, campothecin, actinomycin-D, mitomycin C, or cisplatin. The cell may be a human tumor cell. The plasmid may have a cytomegalovirus promoter and an SV40 polyadenylation signal.

Gregory et al. (see the entire article) taught a method of reducing the growth rate of a human cell tumor by contacting the cells of a tumor with a gene encoding a functional p53 protein in an adenoviral vector which was deleted in E1A or E1B and which contained a CMV promoter.

Gregory et al. did not teach contacting the human tumor cell with a DNA damaging agent, nor that the vector may be a plasmid with an SV40 polyadenylation signal.

Wills et al. (see the entire article) taught a method of killing a tumor cell comprising contacting a tumor cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, gamma irradiation, or etoposide. An adenoviral vector expressing the p53 gene may be deleted in E1A or E1B and which contained a CMV promoter. The p53 gene was expressed in tumors in animal models.

Lowe et al. (see the entire article) taught a method of killing a tumor cell comprising contacting a tumor cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, gamma irradiation, or etoposide. The p53 gene was in a non-viral vector, which may be a naked DNA plasmid.

Clarke et al. (see the entire article) taught a method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, gamma irradiation, or etoposide. The p53 gene was in a non-viral vector, which may be a naked DNA plasmid.

Tischler et al. taught contacting tumor cells with a gene expressing a functional p53 gene and a DNA damaging agent where the DNA damaging agent was X-rays, UV irradiation, gamma irradiation, microwaves, adriamycin, 5-flourouracil, etoposide, campothecin, actinomycin-D, mitomycin C, or cisplatin.

The use of an SV40 polyadenylation signal sequence and encapsulation of a vector in a liposome are arbitrary choices within the purview of an ordinary skilled artisan and, lacking unexpected results, are not deemed to make a patentable distinction to the instant claimed invention.

Optimization of the invention as in claims 86-91 and 111-120 is an obvious process which carries no patentable weight in the absence of evidence that such optimization provides unexpected results.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method of reducing the growth rate of a human tumor cell by contacting the cells of a tumor with a gene encoding a functional p53 protein in an adenoviral vector expressing the p53 gene where the adenoviral vector was deleted in E1A or E1B and which contained a CMV promoter of Gregory et al. with the method of killing a tumor cell comprising contacting a tumor cell with a p53 gene and a DNA damaging agent, where the DNA damaging agent may be X-rays, gamma irradiation, or etoposide where the p53 gene was in a non-viral vector, which may be a naked DNA plasmid of Lowe et al. or Clarke et al. and Tischler et al because they were all investigating the effects of p53 on cell death. The adenoviral vectors of Will et al. and Gregory et al. were obvious alternatives to the plasmid vectors of Lowe et al. or Clarke et al. or Tischler et al. for the purposes of introducing the p53 gene into cells to study cell death.

One of ordinary skill in the art would have been motivated to combine the method of Gregory et al. with the method Lowe et al. or Clarke et al. and Tischler et al because they were all investigating the effects of p53 on cell death. Gregory et al. stated that the "[m]utation or loss of p53 tumor suppressor gene is the most frequently detected genetic alteration associated with human malignancies. And introduction of wild-type p53 into altered p53 human tumor cells suppresses their tumorigenic properties and in some cases apoptosis". Wills et al. and Clarke et al. taught the introduction of wild-type p53 into a p53-deficient tumor cell produced apoptosis when the cell had been exposed to a DNA damaging agent. This was confirmed *in vivo* in a

mouse model system. Tischler et al. extended the list of DNA damaging agents which may be used in conjunction with the introduction of a p53 gene to produce apoptosis. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Gregory et al. in view of Lowe et al., Clarke et al., Wills et al., and Tischler et al.

26. Claims 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gregory et al. in view of Lowe et al., Clarke et al., Wills et al., and Tischler et al. as applied to claims 1-26, 32-41, 46-61, 77-79, 83-91, 96-101, 111-120, 127-130 above, and further in view of the Stratagene Catalogue.

Claims 42-45 are drawn to a kit which contains a recombinant vector that expresses a functional p53 protein and a pharmaceutical formulation of a DNA damaging agent (which may be cisplatin).

The claims are rejected for all the reasons stated above and because the Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Gregory et al. in view of Lowe et al., Clarke et al., Wills et al., and Tischler et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-

mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantitites you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Conclusion

27. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

April 14, 2001

TERRY MCKELVEY
PRIMARY EXAMINER